1-[2-(2,4-DIMETHYLPHENYLSULFANYL)-PHENYL]PIPERAZINE AS A COMPOUND WITH COMBINED SEROTONIN REUPTAKE, 5-HT_3 AND 5-HT_{1A} ACTIVITY FOR THE TREATMENT OF COGNITIVE IMPAIRMENT

CROSS REFERENCE TO PRIOR APPLICATIONS

This is a continuation application of U.S. application Ser. No. 14/948,775, filed Nov. 23, 2015, which is a continuation application of U.S. application Ser. No. 14/242,337, filed Apr. 1, 2014, now U.S. Pat. No. 9,227,946, issued Jan. 5, 2016, which is a divisional application of U.S. application Ser. No. 12/301,061, filed Aug. 24, 2009, now U.S. Pat. No. 8,722,684, issued May 13, 2014, which is a U.S. National Phase application under 35 U.S.C. §371 of International Patent Application No. PCT/DK2007/050075, filed Jun. 15, 2007, and claims the benefit of Danish Patent Application No. PA 2006 00824, filed Jun. 16, 2006; U.S. Provisional Application No. 60/805,014, filed Jun. 16, 2006; Danish Patent Application No. PA 2006 01223, filed Sep. 22, 2006; U.S. Provisional Application No. 60/826,666, filed Sep. 22, 2006; Danish Patent Application No. PA 2006 01384, filed Oct. 25, 2006; U.S. Provisional Application No. 60/862,826, filed Oct. 25, 2006; and Danish Patent Application No. PA 2007 00427, filed Mar. 20, 2007, all of which are incorporated by reference herein. The International Application published in English on Dec. 21, 2007 as WO 2007/144005 under PCT Article 21(2).

FIELD OF THE INVENTION

The present invention relates to compounds, which exhibit serotonin reuptake inhibition activity combined with an activity on the serotonin receptor 1A (5-HT_{1A}) and the serotonin receptor 3 (5-HT_3), and which as such are useful in treatment of CNS related diseases.

BACKGROUND OF THE INVENTION

Selective serotonin reuptake inhibitors (SSRI) have for years been the first choice therapeutics for the treatment of certain CNS related diseases, in particular depression, anxiety and social phobias because they are effective, well tolerated and have a favourable safety profile as compared to previously used compounds, i.e. the classical tri-cyclic compounds.

Nonetheless, therapeutic treatment using SSRI is hampered by a significant fraction of non-responders, i.e. patients who do not respond or only respond to a limited extent to the SSRI treatment. Moreover, typically an SSRI treatment does not begin to show an effect until after several weeks of treatment.

In order to circumvent some of these shortcomings of SSRI treatment, psychiatrists sometimes make use of augmentation strategies. Augmentation of antidepressants may be achieved e.g. by combination with mood stabilisers, such as lithium carbonate or triiodothyronin, or by the parallel use of electroshock.

It is known that a combination of inhibition of the serotonin transporter (SERT) with an activity on one or more serotonin receptors may be beneficial. It has previously been found that the combination of a serotonin reuptake inhibitor with a compound having 5-HT_{2C} antagonistic or inverse agonistic effect (compounds having a negative efficacy at the 5-HT_{2C} receptor) provides a considerable increase in the level of 5-HT (serotonin) in terminal areas, as measured in microdialysis experiments (WO 01/41701). This would imply a shorter onset of antidepressant effect in the clinic and an augmentation or potentiation of the therapeutic effect of the serotonin reuptake inhibitor (SRI).

Similarly, it has been reported that the combination of pindolol, which is a 5-HT_{1A} partial agonist, with a serotonin reuptake inhibitor gives rise to fast onset of effect [*Psych. Res.*, 125, 81-86, 2004].

CNS related diseases, such as e.g. depression, anxiety and schizophrenia are often co-morbid with other disorders or dysfunctionalities, such as cognitive deficits or impairment [*Scand. J. Psych.*, 43, 239-251, 2002; *Am. J. Psych.*, 158, 1722-1725, 2001].

Several neurotransmitters are presumed to be involved in the neuronal events regulating cognition. In particular, the cholinergic system plays a prominent role in cognition, and compounds affecting the cholinergic system are thus potentially useful for the treatment of cognitive impairment. Compounds affecting the 5-HT_{1A} receptor and/or the 5-HT_3 receptor are known to affect the cholinergic system, and they may as such be useful in the treatment of cognitive impairment.

Hence, a compound exerting 5-HT_{1A} and/or 5-HT_3 receptor activity would be expected to be useful in the treatment of cognitive impairment. A compound which moreover also exerts SERT activity would be particular useful for the treatment of cognitive impairment in depressed patients as such compound would also provide a fast onset of the treatment of the depression.

WO 03/029232 discloses e.g. the compound 1-[2-(2,4-dimethylphenyl-sulfanyl)phenyl]piperazine (example 1e) as a compound having SERT activity.

SUMMARY OF THE INVENTION

The present inventors have surprisingly found that 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine exerts a combination of SERT inhibition, 5-HT_3 antagonism and 5-HT_{1A} partial agonism. Accordingly, in one embodiment the present invention provides compound I which is 1-[2-(2,4-dimethylphenylsulfanyl)-phenyl]piperazine and pharmaceutically acceptable salts thereof, provided said compound is not the free base in a non-crystalline form.

In one embodiment, the invention provides the use of compound I in therapy.

In one embodiment, the invention provides a pharmaceutical composition comprising compound I.

In one embodiment, the invention provides therapeutic methods comprising the administration of an effective amount of compound I to a patient in need thereof.

In one embodiment, the invention provides the use of compound I in the manufacture of a medicament.

FIGURES

FIG. **1**: XRPD of crystalline base
FIG. **2**: XRPD of alpha form of hydrobromide salt
FIG. **3**: XRPD of beta form of hydrobromide salt
FIG. **4**: XRPD of gamma form of hydrobromide salt
FIG. **5**: XRPD of hemi hydrate of hydrobromide salt
FIG. **6**: XRPD of the mixture of the ethyl acetate solvate and the alpha form of the hydrobromide salt
FIG. **7**: XRPD of hydrochloride salt
FIG. **8**: XRPD of monohydrate of hydrochloride salt
FIG. **9**: XRPD of mesylate salt
FIG. **10**: XRPD of fumarate salt